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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/063,978	04/21/98	OBREMSKI R	45D-1750(641

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EXAMINER	
HINES, J	
ART UNIT	**PAPER NUMBER**
1645	20

DATE MAILED: 08/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/063,978	Obremski et al.
Examiner	**Art Unit**
Ja-Na Hines	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 21, 2001*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-28* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Amendment Entry

1. The amendment filed May 21, 2001 has been entered. Claims 1-2, 23 and 26 have been amended. Claims 27-28 have been newly added. Claims 1-28 are pending in this office action.

Response to Arguments

2. Applicant's arguments filed May 21, 2001 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-4, 13-19, 21 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) is maintained. Claims 27-28 are drawn to an insoluble support and the binding cpacity of the microspoic sorbent zone is 150um and is about 10^{10} analyte molecules. Ekins et al., (EP 304,202) teach the support is preferably non-porous so that the binding agent is disposed on its surface and may be made of plastic material such as polystyrene, polyolefins or acrylic or vinyl polymers or glass (page 5 lines 1-11). The support may be coated on micro spheres with uniform layers of

binding agents and retained in specific locations or in the form of a sheet or plate which is spotted with an array of dots of binding agents (page 5 lines 12-15). This is advantageous because the configuration of the support means to be such that liquid samples of approximate volumes are readily in contact with the plurality of spaced apart locations marked with the different binding agents (page 5 lines 15-18). The size of the spots are advantageously less than $10mm^2$, preferable less than $1mm^2$ (page 6 lines 5-6). In Example 1, the spots on the support are approximately $1mm^2$ and a sample volume of about 400ml or 2.4×10^{10} molecules of analyte.

Ekins et al., (J. of Clinical Immuno.) teach multianalyte immunoassays. Ambient analyte immunoassays essentially rely on the measurement of antibody occupancy (page 172 para.2). This measures the analyte concentration in the medium to which the antibody is exposed (page 172 para. 2). Figure 4 reveals that when an amount of antibody is exposed to an analyte containing medium the resulting occupancy of antibody binding sites solely reflects the ambient analyte concentration (page 173 para. 1). Analyte binding by antibody clearly causes analyte depletion in the surrounding medium (page 173 para. 1)

Therefore, at the time of applicants invention it would have been obvious to use the technique of allowing for analyte depletion in a sample as taught by Ekins et al., (J. of Clinical Immun.) in the binding assay of Ekins et al., (EP 304,202) because this technique is already well known in the art for determining analyte concentration.

Applicant argues that the microscopic sorbent zones unexpectedly deplete substantially all analyte from the sample and concentrate the analyte onto the small measurement region. Applicant also states that there is an unexpected benefit of high signal-to-background ratio of binding assay by concentrating the signal on the small area of support.

However, Ekins et al., (EP 304,202) teach small sample sizes in individual micro-arrays wherein the concentration of binding reagent may range from 10^5 to 10^{10} molecules of binding agent. Understanding that the recognition of such small amounts of binding agents is permissible, next it is feasible to place the binding agent required for a single concentration measurement on a very small area of a solid support. A high coating density is generally desirable to maximize signal/noise ratios. Ekins et al., (J. of Clinical Immuno.) teach measuring the analyte concentration in the medium to which the antibody is exposed wherein the analyte binding by antibody clearly causes analyte depletion in the surrounding medium. Therefore, Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) teach microscopic sorbent zones that unexpectedly deplete substantially all analyte from the sample and concentrate the analyte onto the small measurement region. Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) teach using large amounts of antibody to capture analyte in a small sample, which substantially depletes the sample of analyte. Furthermore, applicants mere statement that unexpected results were achieved is unpersuasive. Applicants failed to provide scientific data showing that unexpected results were achieved when using large amounts of antibody to bind analyte.

Applicant argues that both references require only an insignificant proportion of any analyte present in the liquid sample becomes bound to the binding agent, and that the references teach away from analyte depletion. However, Ekins et al., (J. of Clinical Immuno.) teach "Analyte binding by antibody clearly causes analyte depletion in the surrounding medium (page 173 para. 1). Figure 4 shows antigen bound concentrations as high as 100% when using higher antibody concentration. The instant specification defines substantial depletion to be at least about 60% of analyte. Thus, Ekins et al., (EP 304,202) in view of Ekins et al., (J. of Clinical Immuno.) teach substantial analyte depletion as defined by the instant application.

Applicants argue that it is unexpected that microscopic sorbent zones can substantially deplete analyte from a macroscopic, 100ul, sample volume. However, Ekins et al., (EP 304,202) teach sample sizes of the order of one or a few milliliters, i.e., from about 100ul or less, however circumstances may arise when larger volumes are assayed and the geometry can be adjusted (page 6 lines 27-29). Example 1, the spots on the support are approximately $1mm^2$ and a sample volume of about 400ml or 2.4×10^{10} molecules of analyte. Therefore, at the time of applicants invention it would have been obvious to use the technique of allowing for analyte depletion in a sample as taught by Ekins et al., (J. of Clinical Immun.) in the binding assay of Ekins et al., (EP 304,202) because this technique is already well known in the art for determining analyte concentration.

Applicants argue that their assay is drawn to a binding assay for sensing analyte mass, whereas the references teach analyte concentration. However, the references teach the same method steps, use the same laser microscopy techniques to assay the analyte, and provides results in terms of molecules bound. Applicant's use of analyte mass appears to be identical to the prior art's reference to analyte concentration. The laser analysis of applicants analyte mass does not provide the weight of the analyte, but provides the concentration, just as the prior art references. Therefore, applicants argument that the assays are providing different measurements is unpersuasive.

4. Claims 1-4, 13-19, 21 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of Ekins et al., (Analytica Chimica Acta.) is maintained. Claims 27-28 are drawn to an insoluble support and the binding capacity of the microspoic sorbent zone is 150um and is about 10^{10} analyte molecules. However, Ekins et al., (EP 304,202) teach the limitations of claims 27-28 and have been discussed above.

No more than routine skill is required to implement well known techniques such as analyte depletion into the binding assay of Ekins et al. (EP 304,202). Therefore, at the time of applicants invention it would have been obvious to use the technique of allowing for analyte depletion in a sample as taught by Ekins et al., (Analytica Chimica Acta.) in the binding assay of Ekins et al., (EP 304,202) because this technique is already well known in the art for determining analyte concentration.

Applicants argue that the combination of references do not teach substantial depletion of the analyte from the sample. However, Ekins et al., (EP 304,202) has been discussed above. Ekins et al., (Analytica Chimica Acta.) teach the development of microspot multi-analyte ratiometric immunoassays using dual fluorescent labeled antibodies. Figure 4 reveals that when an amount of antibody is exposed to an analyte containing medium the resulting occupancy of antibody binding sites solely reflects the ambient analyte concentration wherein antigen bound is about 100%. Binding by antibody clearly results in a depletion of the amount of analyte in the surrounding medium. Therefore, Ekins et al., (EP 304,202) in view of Ekins et al., (Analytica Chimica Acta.) teach substantial depletion of analyte in the surrounding medium.

No more than routine skill is required to implement well known techniques such as analyte depletion into the binding assay of Ekins et al., (EP 304,202). Therefore, at the time of applicants invention it would have been obvious to use the technique of allowing for analyte depletion in a sample as taught by Ekins et al., (Analytica Chimica Acta.) in the binding assay of Ekins et al., (EP 304,202) because this technique is already well known in the art for determining analyte concentration.

5. Claims 5-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) and either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.), in further view of Ullman et al., (US Patent 5,512,659). Ekins et al.(EP 304,202), Ekins et al., (J. of Clinical Immuno.) and Ekins et al., (Analytica Chimica Acta.) have been discussed.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious at the time of applicants invention to have used the first binding partner, conjugate, biotin-avidin labels and biotinylated antibodies as taught by Ullman et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) because Ullman et al., teaches that these methods are more versatile and convenient than the known methods.

6. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202), in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in further view of Waggoner et al., US Patent (5,368,486) is maintained. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

Ekins et al., (EP 304,202), Ekins et al., (J. of Clinical Immuno.), Ekins et al., (Analytica Chimica Acta.) have been discussed previously however, none of the three Ekins et al., references teach the use of cyanine dyes. Waggoner et al., (US Patent 5,268,486) teach the use of fluorescent cyanine and related polymethine dyes which can be used for detecting the presence of certain proteins. No more than routine skill would have been required to use cyanine dyes as taught by Waggoner et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) because Waggoner et al., teach that these cyanine dyes are intrinsically more fluorescent; have improved photostability; improved water solubility; can label a wide variety of biological materials; and subject to a variety of excitation wavelengths using lasers.

7. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in view of Waggoner et al., US Patent (5,368,486) in further view of Lee et al., (US Patent 5,453,505) is maintained. Ekins et al., (EP 304,202), Ekins et al., (J. of Clinical Immuno.), Ekins et al., (Analytica Chimica Acta.) and Waggoner et al., have all been discussed previously however, none teaches the use of Cy5 or Cy7. In this case, applicants argue that there is no suggestion to combine the references, however the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in

the references themselves or in the knowledge generally available to one of ordinary skill in the art.

Lee et al., teaches the most stable dye was found to be the dye with the shortest wavelength, Cy5 whose structure contains five methine groups, while the remaining dyes contain seven methine groups, such as Cy7 which has similar stability. Accordingly, it would have been obvious at the time of applicants invention to have used Cy5 or Cy7 as taught by Lee et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.), and Waggoner et al., US Patent (5,368,486), because Lee et al., teaches a reduced tendency to aggregate and enhanced photostability.

8. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) in view of Northrup et al (US Patent 5,639,423) is maintained. Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) have been discussed previously. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

In this case, it would have been obvious at the time of applicants invention to use the well

known method of dispensing material using a jet printer as taught by Northrup et al., in the method of Ekins et al., (EP 304,202) in view of either Ekins et al., (J. of Clinical Immuno.) or Ekins et al., (Analytica Chimica Acta.) because Northrup et al., teaches that the method is especially advantageous for biochemical reactions.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines

August 10, 2001

LYNETTE R. F. SMITH
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